Questions and Answers About ALTS

1. What is ALTS?

ALTS is a clinical trial designed to find the best way to manage the mild abnormalities that often show up on the routine screening tests for cervical cancer commonly known as Pap tests. The study, organized and funded by the National Cancer Institute (NCI), began enrolling participants in November 1996. Enrollment was completed in late 1998. The study results should be published in about 3 years.

2. What does the name mean?

ALTS is an acronym for the ASCUS/LSIL Triage Study. ASCUS and LSIL are acronyms for the two mild abnormalities detected by Pap tests. ASCUS stands for atypical squamous cells of undetermined significance and LSIL for low-grade squamous intraepithelial lesions (see question 10 for more on ASCUS and LSIL).

Because the study is evaluating different management options, ALTS also refers to Alternatives in Women's Health Care.

3. Why did NCI organize ALTS?

NCI expects the trial to resolve the controversy over what physicians and women should do about ASCUS and LSIL diagnoses. Most of these mild abnormalities go away without treatment. But doctors today have no way to tell the difference between those that will go away and those that will progress to a precancerous condition or cancer.

Many physicians in the United States now opt for aggressive management of these mild abnormalities, referring women to a colposcopic exam (see question 6) with biopsies of suspicious abnormalities. This approach carries a small risk of medical complications and is expensive. Other doctors opt for a more conservative, wait-and-see approach, recommending frequent, repeat Pap tests to see if the abnormalities go away without treatment.

ALTS is evaluating different ways of managing Pap test abnormalities that may be as effective as colposcopy but less invasive and costly. Benefits include fewer medical complications resulting from aggressive treatment and reduced patient anxiety. In

addition, the potential cost savings from alternative strategies are significant. Assuming that there are 3,250,000 ASCUS and LSIL diagnoses in the United States per year and that the cost of colposcopy and biopsy follow-up is an average $1,200 per case, the total annual cost of aggressive management is $3.9 billion.

4. What is a clinical trial?

In cancer research, a clinical trial is a medical study with people. It is designed to show how a particular intervention—for instance, a preventive measure, a diagnostic test, or a treatment—affects the people who receive it. The guidelines for the intervention are specified in a document called a protocol.

5. Who is conducting this trial and where? How many women are participating?

Researchers are conducting ALTS at four major medical centers: the University of Alabama at Birmingham, Alabama; the University of Oklahoma in Oklahoma City, Oklahoma; Magee-Women's Hospital in Pittsburgh, Pennsylvania; and the University of Washington in Seattle, Washington.

The four ALTS clinical centers worked with physicians and clinics in their areas to enroll patients in the study. A total of about 7,200 women were enrolled.

6. How is the study designed?

ALTS is comparing three different ways of managing ASCUS and LSIL abnormalities. Women who enrolled in the study were divided into those with ASCUS and those with LSIL diagnoses. The patients in each category were assigned to one of three groups or study arms. Assignments were made randomly; therefore, participants had an equal chance of being assigned to each of the three groups.

Immediate Colposcopy: Women in this arm were referred to a health professional who used a colposcope, a magnifying instrument, to examine the cervix and identify abnormal tissue for biopsy and treatment, if necessary. This is the aggressive management option used commonly in the United States. Women in this arm, as in the others, are being monitored with a repeat Pap test every 6 months.

Conservative Management: Women in this arm are being closely followed with repeat Pap tests (or, to use the more scientific term, *cervical cytology*[*]) every 6 months. Patients have a colposcopy and a biopsy if the repeat Pap test results suggest they have more severe abnormalities. This conservative approach is now common in Canada and in some European countries.

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*ALTS researchers use the term cytology rather than Pap test because in this trial they are using a new technique for collecting cervical cells and transferring them to slides, which is called liquid-based cytology or thin-layer slide preparation (see question 13).

HPV Triage: Women in this arm are being managed based on results of the Pap test plus a test for the human papillomavirus (HPV), which causes most cervical cancers. If their Pap test shows more severe abnormalities or if their cervical cells contain DNA from certain HPV types associated with cancer, they undergo immediate colposcopy. Otherwise they are followed like participants in the Conservative Management arm. The HPV Triage arm tests the hypothesis that HPV testing is effective at triage (i.e., assigning patients to one approach or the other).

7. How do the researchers make sure they do not miss any severe abnormalities on any arm of the study?

Several safety precautions are built into the study.

Quality control groups: Three independent quality control groups review the accuracy of the Pap/cytology tests, the HPV tests, and colposcopies.

Cervicography: At enrollment and each follow-up visit, participants have cervicography—a technique that allows researchers to examine enlarged photographs of the cervix. Cervigrams are read by certified expert evaluators. Any participant whose cervigram is judged worrisome has a colposcopy.

Data and Safety Monitoring Committee: Appointed by the NCI, this independent committee of experts reviews the collected data periodically and provides final authorization for the continuation and conduct of the trial.

Final colposcopy: At the end of the 3-year follow-up period, all participants are examined by colposcopy (and biopsy as appropriate) to ensure that they do not leave the trial with undiagnosed and untreated lesions.

8. What specifically do the researchers expect to learn from ALTS?

Researchers will compare the three different groups to learn 1) how effective each management option is in early detection of the serious abnormalities that can progress to cancer; 2) how acceptable each option is to patients; and 3) how cost effective each option is. These are the trial's three main objectives, the "endpoints" on which the researchers collect data.

In addition, ALTS researchers will analyze findings to learn more about mild cervical abnormalities and their relationship to cancer. For instance, they hope to gain information about immune system factors that may help determine whether a mild abnormality goes away without treatment or progresses to a more severe abnormality. The investigators will also evaluate the use of several new technologies for collecting and reading cervical cells (see questions 12–15).

9. What are the different Pap test diagnoses?

Most laboratories in the United States now use the Bethesda System for reporting Pap test results. This system divides cervical cell abnormalities into three major categories.

ASCUS—atypical squamous cells of undetermined significance. Squamous cells are the thin flat cells that form the surface of the cervix.

LSIL—low-grade squamous intraepithelial lesion. The word lesion refers to an area of abnormal tissue; intraepithelial means that the abnormal cells are present only in the surface layer of cells.

HSIL—high-grade squamous intraepithelial lesion.

ASCUS and LSIL are considered mild abnormalities. HSIL is more severe and has a higher likelihood of progressing to invasive cancer.

10. How common are Pap test abnormalities?

About 50 million Pap tests are performed each year in the United States with 5 to 10 percent showing mild abnormalities, either ASCUS or LSIL. A rough estimate puts the number of ASCUS diagnoses at 2,000,000 a year and LSIL at 1,250,000 a year. In addition, an estimated 300,000 women are diagnosed with the more severe abnormality, HSIL.

11. What are the traditional methods of collecting and reading cells from the cervix?

In a traditional Pap test, cells are collected from the cervix with a spatula and brush or swab, which is then wiped across a glass slide. The slide is sent to a laboratory, where a cytologist examines it under a microscope for any signs of abnormality.

12. Why are new methods being developed?

The conventional methods, though effective in the majority of cases, do not have 100 percent accuracy. About half of the false negatives (missed abnormalities) are due to inadequate specimen collection and the other half to a failure to identify the abnormal cells or to interpret them accurately, according to the Consensus Development Conference on Cancer of the Cervix convened by the National Institutes of Health (NIH) in April 1996. New methods of collecting and reading cervical cells are under investigation to reduce the false negative rate.

13. What are the new methods?

Automated thin-layer slide preparation techniques. To prepare thin-layer slides, clinicians collect cervical cells with a brush or other collection instrument and then rinse the instrument in a vial of liquid preservative (this technique is also known as liquid-based cytology). The vial is sent to the laboratory where the cells are extracted and placed evenly on slides by automated equipment. Preliminary results suggest that this method is comparable to PAP smears for detection of significant abnormalities.

Automated readers. With this technology, an automated microscope conveys a cellular image to a computer, where it is analyzed. In fall 1995, the FDA approved two automated readers for the rescreening of cervical cells evaluated as normal on the initial screen. They are AutoPap made by NeoPath, Incorporated (Redmond, Washington) and Papnet made by Neuromedical Systems (Suffern, New York).

HPV and HPV Testing

14. What is human papillomavirus (HPV)?

HPV is a group of at least 70 different types of viruses. At least 23 types infect the cervix, and more than a dozen of these have been linked to cervical cancer (some other types cause warts). The cancer-associated types of HPV are called high-risk types. Both high-risk and low-risk types can cause abnormalities in the cervix, but it appears that abnormalities associated with high-risk types progress more often to cervical cancer.

15. Who is at risk for HPV infection?

HPV infection is more common in younger age groups, particularly in women in their late teens and twenties. Because HPV is spread mainly through sexual contact, risk increases with number of sexual partners. Women who become sexually active at a young age, who have multiple sexual partners, and whose sexual partners have other partners are at increased risk. Nonsexual transmission is also possible. The virus often disappears but may remain detectable for years after infection.

16. What HPV types are linked to cancer?

HPV-16 is the type most frequently found in precancerous and cancerous lesions in all geographic areas around the world that have been studied. Next in prevalence is HPV-18. Other types considered high-risk are HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Together these account for nearly 90 percent of HPV infections in cases of HSIL and cervical cancer.

17. Does HPV cause cervical cancer?

Yes. The NIH Consensus Conference on Cancer of the Cervix and the World Health Organization have concluded that there is a cause and effect relationship between HPV and cervical cancer. Scientists continue to study other factors that may also be required for the development of cancer, such as changes in the immune system.

18. Does infection with a cancer-associated type of HPV always lead to a precancerous condition or cancer?

No. Most infections appear to go away on their own without causing any kind of abnormality. However, infection with cancer-associated HPV types may increase the risk that mild abnormalities will progress to more severe abnormalities or cervical cancer. With regular follow-up care by trained clinicians, women with precancerous cervical abnormalities should not develop invasive cervical cancer.

19. Do LSIL and HSIL ever develop in the absence of HPV infection?

Yes, but rarely. The vast majority of LSIL and HSIL have detectable HPV DNA. Researchers think that less than 10 percent of all cases have no HPV DNA.

20. What test is ALTS using to detect cancer-associated HPV types?

In ALTS, the HPV test used to detect cancer-associated HPV types is called the Hybrid Capture Microplate (HCM) test. HCM is a nonradioactive liquid hybridization method that tests for HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. This test is a product of Digene Diagnostics (Silver Spring, Maryland).

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<u>Sources of National Cancer Institute Information</u>

Cancer Information Service

Toll-free: 1–800–4–CANCER (1–800–422–6237)
TTY (for deaf and hard of hearing callers): 1–800–332–8615

NCI Online

Internet

Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service
Dial 301–402–5874 and listen to recorded instructions.

This fact sheet was reviewed on 9/2/99